The Value of Occult Disease in Resection Margin and Lymph Node After Extrapleural Pneumonectomy for Malignant Mesothelioma

Tommaso Claudio Mineo, Vincenzo Ambrogi, Eugenio Pompeo, Alfonso Baldi, Franco Stella, Paolo Aurea and Mario Marino

Ann Thorac Surg 2008;85:1740-1746
DOI: 10.1016/j.athoracsur.2008.01.088

The Value of Occult Disease in Resection Margin and Lymph Node After Extrapleural Pneumonectomy for Malignant Mesothelioma

Tommaso Claudio Mineo, MD, Vincenzo Ambrogi, MD, Eugenio Pompeo, MD, Alfonso Baldi, MD, Franco Stella, MD, Paolo Aurea, MD, and Mario Marino, MD

Department of Thoracic Surgery, Policlinico Tor Vergata University, Rome, Anatomic Pathology Section, Department of Biochemistry and Biophysic "F. Cedrangolo," Second University of Naples, Naples, and General and Thoracic Surgery Department, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy

Background. **The purpose of this study was to examine the prognostic impact of occult disease after extrapleural pneumonectomy for malignant mesothelioma.**

Methods. **We reviewed the resection margin and node specimens from 41 consecutive patients undergoing extrapleural pneumonectomy for malignant pleural mesothelioma in different institutions between 1985 and 2004. The specimens were reassessed by immunohistochemical staining with anticalretinin and antimesothelin monoclonal antibodies, and results were used to draw Kaplan–Meier survival curves and perform Cox regression analyses.**

Results. **Histologic examination showed 34 epithelioid, 4 biphasic, and 3 sarcomatoid subtypes. Results of postoperative TNM staging were that 14 patients were in stage I, 6 were in stage II, and 21 were in stage III. One patient died during the early postoperative period. Median survival was 13 months. Survival was affected by nonepithelial histologic type ($p = 0.001$), TNM stage ($p = 0.007$), positive resection margins ($p = 0.002$), and N disease ($p = 0.01$). Immunohistochemistry revealed occult positive resection margins in 6 patients, not correlated with T stage. Microscopic N disease was discovered in 5 patients, of whom 2 had their nodes retrieved through cervical mediastinoscopy. No correlation with nodal diameter was found. In all patients microscopic N disease could have been accessible through mediastinoscopy. Overall, the presence of occult disease was diagnosed in 5 new patients and influenced survival more than any other variable, both at univariate ($p < 0.001$) and multivariate Cox regression analysis ($p < 0.0001$; odds ratio, 5.4; 95% confidence interval, 3 to 15).**

Conclusions. **In malignant pleural mesothelioma, the presence of occult disease in resection margins and lymph nodes can be identified by immunohistochemistry and significantly influences the prognosis. Cervical mediastinoscopy is useful in all patients considered for radical resection, but all specimens should be processed with immunohistochemical staining.**

(Ann Thorac Surg 2008;85:1740–6)

Malignant pleural mesothelioma is a rare, highly aggressive tumour with a very poor prognosis [1–3]. Despite extensive surgical removal provided by extrapleural pneumonectomy, patients relapsed rapidly. Therefore, most treatment regimens have focused on radiation therapy, chemotherapy and immunotherapy multimodality treatment [4], or neoadjuvant chemotherapy [5].

According to these observations it is conceivable that some residual tumor may persist in spite of aggressive and extended surgery. In malignant pleural mesothelioma, the main sites of recurrence are represented by either local or mediastinal intrathoracic seeding [6]. These tumoral nests are likely located in proximity of resection margins or in mediastinal nodes not adequately assessed at the time of thoracotomy. Indeed, positive resection margins and mediastinal lymph node metastases have been identified as poor prognostic factors in many published series [3–12]. However, some patients experience a poor outcome despite a histologically proven complete surgical resection. We have recently investigated the role of occult residual or micrometastases in lung neoplasms detected by immunohistochemistry, and we found that their evidence may justify unpredictable recurrence patterns [13]. Therefore, we have extended our observations to malignant pleural mesothelioma.

The aim of the present study was to examine, in a group of patients undergoing extrapleural pneumonectomy, the prognostic impact of occult disease in resection margins and mediastinal lymph nodes identified after immunohistochemical staining with anticalretinin and antimesothelin monoclonal antibodies [14]. The role of preoperative cervical mediastinoscopy in patient selection was also investigated.

Accepted for publication Jan 28, 2008.

Address correspondence to Dr Mineo, Cattedra di Chirurgia Toracica, Università degli Studi di Roma Tor Vergata, Policlinico Universitario Tor Vergata, Roma, Via Oxford, 81, Rome, 00133, Italy; e-mail: mineo@med.uniroma2.it.

Published by Elsevier Inc

0003-4975/08/$34.00
doi:10.1016/j.athoracsur.2008.01.088

Patients and Methods

Patients

From 1985 to 2004 inclusive, 41 consecutive patients, 30 men and 11 women, median age 58 ± 12 years (range, 41 to 70 years), intentionally underwent radical extrapleural pneumonectomy (24 right and 17 left) in different institutions. All clinical, laboratory, and histologic data were retrospectively reviewed.

Permission for this retrospective study and authorization for tissue samples reanalysis was obtained from the institutional review boards of each institution where the operations were performed.

Patients considered eligible for extrapleural pneumonectomy were those with a confirmed preoperative diagnosis of malignant pleural mesothelioma at stage T1 through T3 according to the International Mesothelioma Interest Group [8], with a Karnofsky index equal to or greater than 90%, and without major organ dysfunction. Physiologic reasons for inoperability were a predicted postoperative forced expiratory volume in 1 second less than 40% of the predicted value or less than 1 L and evidence of contralateral hypoperfused lung (less than 55% of the right or 45% on the left). Other criteria of exclusion were room air arterial partial pressure of carbon dioxide greater than 45 mm Hg or arterial partial pressure of oxygen less than 65 mm Hg, an estimated cardiac ejection fraction less than 0.45, or right ventricular dilatation.

All patients had undergone computed tomographic scan of the thorax and upper abdomen and contrast-enhanced magnetic resonance imaging. This study group population was gathered before the arrival of a positron emission tomography scanner. Resectability was defined by tumor confined to one hemithorax, with the absence of mediastinal organ or full-thickness pericardial or myocardial involvement, absence of diffuse or multifocal chest wall disease, transdiaphragmatic extension, or spread directly into the spine, hence excluding stage T4 disease. Preoperative cervical mediastinoscopy was performed whenever computed tomographic scan evidenced enlarged upper mediastinal lymph nodes (a maximum diameter greater than 15 mm). The evidence of positive mediastinal lymph nodes was considered an absolute exclusion criterion for extrapleural pneumonectomy.

Surgical Technique

Briefly, extrapleural pneumonectomy was performed through an extended posterolateral thoracotomy, in most cases through the sixth intercostal space with a counter-incision in the eighth one. The procedure included en bloc excision of the lung, pleura, hemipericardium, and hemidiaphragm. The pleura was bluntly dissected along the extrapleural plane, saving the endothoracic fascia whenever possible. In sites of localized infiltration and of previous biopsies, the chest wall was excised en bloc with the specimen or subsequently resected. The mediastinal pleura was dissected from the apex toward the hilum. The pericardium was opened and widely excised on both the anterior and posterior sides. Vessels and bronchus were approached as in any intrapericardial pneumonectomy and sutured using stapling devices. The diaphragm was completely separated from the peritoneum and resected at its insertion to the chest wall. Incidental peritoneal tears were sutured. The diaphragm was replaced by a Gore-Tex dual mesh (W.L. Gore & Assoc, Flagstaff, AZ), and the pericardium was reconstructed with a Gore-Tex patch (W.L. Gore & Assoc). Patients found to have a multicentric macroscopic invasion of the chest wall or mediastinal structures were not resected. All mediastinal lymph nodes were routinely resected to allow accurate surgical staging of the disease.

Conventional Pathologic Examination

During the immediate postoperative period, each specimen was routinely processed as follows. First, the surgeon conducted a gross examination immediately after the procedure, indicating potential areas of incomplete resection. Second, the pathologist macroscopically evaluated the specimen to determine any areas with obvious evidence of residual tumor, paying special attention to the sites indicated by the surgeon. Third, each suspect area was separately embedded in wax and stained for microscopic examination with traditional hematoxylin and eosin. In addition, approximately 20 sections were randomly taken from each specimen in correspondence of selected pleural sites: anterior, lateral, and posterior costophrenic sinus, pericardiophrenic sinus, anterior and posterior mediastinal pleura, and vertebral groove. The bronchial stump, pericardium, and diaphragm were routinely examined for microscopic margins. A positive margin was used to target direct adjuvant radiation treatment. Each lymph node was embedded in wax and sections were stained with hematoxylin and eosin for microscopic examination to determine the presence of metastatic tumor. All embedded samples were stored and were available for future reanalysis.

Adjuvant Therapy

Adjuvant chemotherapy and radiotherapy always followed the surgical procedure. The chemotherapy regimen usually consisted of four to six cycles of cisplatin (100 mg/m^2) given at day 15, and etoposide (120 mg/m^2) administered on days 1, 2, and 3 or, since 1996, gemcitabine (1 g/m^2) administered on days 1, 8, and 15. Cisplatin was infused for 1 hour after intravenous hyperhydration with 2,000 mL of saline solution plus potassium chloride. Etoposide or gemcitabine were administered as a 30-minute intravenous infusion diluted with 250 mL of saline solution. Treatment was discontinued in case of disease progression or intolerable toxicity. Functional assessment (ie, complete and differential blood cell counts, urea nitrogen, creatinine clearance, bilirubin, and liver enzymes) was repeated before each cycle. Dose reduction and delay in therapy were established according to hematologic and nonhematologic toxicity, scored according to the common toxicity criteria (from 0 = no toxicity to 4 = maximal toxicity) [11]. Chemotherapy was started between 4 and 10 weeks after extrapleural pneu-

monectomy depending on the postoperative recovery. Treatment was repeated every 4 weeks.

Radiation therapy usually followed the cycles of chemotherapy. External beam radiotherapy was delivered with an energy ranging from 4 to 15 MV. The total radiation doses to the hemithorax and mediastinum were usually 30 and 40 Gy, respectively, divided into 1.5 Gy fractions. A boost dose (14 Gy in 2 Gy fractions) was always delivered to areas with gross residual disease or positive resection margins, and to metastatic lymph nodes.

Clinical Follow-Up

Whenever possible, clinical outcome was directly assessed during a dedicated session of follow-up outpatient clinic. Alternatively, basic information was retrieved by medical records or general practitioner or patients' interviews by telephone call. Cross-sectional contact for all surviving patients was performed on September 2006. Because clinical symptoms and radiographic studies available during the beginning of the study period were not sensitive enough to accurately diagnose early recurrence, the disease-free interval was not evaluated. Therefore, survival was the major end point of this study. The survival duration was measured from the date of extrapleural pneumonectomy until the date of the patient's last follow-up contact or death.

Immunohistochemical Studies

All the included specimens for resection margin assessment and all extrapleural nodes available from these patients were reviewed after immunohistochemical staining with anticalretinin and antimesothelin monoclonal antibodies. Immunostaining was performed on formalin-fixed, paraffin-embedded tissue sections using the avidin-biotin-peroxidase method. Appropriate sections were cut 4 μm thick and air-dried overnight at 37°C. Sections were then stripped of paraffin with xylene and rehydrated in titrated ethanol series. Endogenous peroxidase activity was blocked with a 10-minute immersion in 0.3% hydrogen peroxide in methanol, followed by a single wash in phosphate-buffered saline solution (pH 7.4). The primary antibodies used in each case were the following: anticalretinin antibody (Swant, Bellinzona, Switzerland; 1:1,500 dilution) and the mesothelin 5B2 monoclonal antibody (Novocastra Laboratories, Newcastle-upon-Tyne, UK; 1:20 dilution). The immunostaining was developed using 3,3′-diaminobenzidine as the chromogen. Negative control sections included nonimmune mouse or rabbit serum as a substitute for the primary antibody. Immunoreactivity was scored as negative (no immunostaining) or positive by an experienced pathologist (A.B.). Cases were considered positive whenever both antigens were detected in at least five cells demonstrating positive immunostaining and morphology compatible with mesothelioma.

Statistical Analysis

Reassessed lymph node status was used to draw new Kaplan–Meier survival curves. Univariate analysis was performed by means of the Kaplan–Meier life-table method to determine the effects of demographic and pathologic variables. Variables included age greater or less than 65 years, side of tumor, sex, smoking history,

Table 1. Univariate Analysis of Main Clinicopathologic Variables

Variable	Frequency	Median Survival (mo)[a]	*p* Value
Age (≥65 vs < 65)	10 vs 31	12 vs 15	0.07
Sex (male vs female)	26 vs 15	11 vs 14	0.38
Performance status (90 vs 100)	12 vs 29	11 vs 15	0.12
Cigarette use (yes vs no)	27 vs 14	13 vs 13	0.78
Asbestos exposure (yes vs no)	31 vs 10	12 vs 13	0.55
Chest pain (yes vs no)	23 vs 18	14 vs 12	0.41
Dyspnea (yes vs no)	30 vs 11	11 vs 13	0.65
Cough (yes vs no)	15 vs 26	13 vs 13	0.87
Side (right vs left)	24 vs 17	11 vs 14	0.55
Chemotherapy regimen (etoposide vs gemcitabine)	15 vs 26	12 vs 14	0.44
Final histology (sarcomatoid and biphasic vs epithelial)	7 vs 34	8 vs 19	0.001
Pathologic T stage (T3 vs T2 vs T1)	9 vs 12 vs 20	9 vs 10 vs 19	0.26
Stage (III vs II vs I)	21 vs 6 vs 14	8 vs 10 vs 20	0.007
Resection margins conventional staining (positive vs negative)	16 vs 25	12 vs 19	0.002
Resection margins immunohistochemistry staining (positive vs negative)	22 vs 19	9 vs 22	<0.0001
N disease conventional staining (positive vs negative)	12 vs 29	10 vs 19	0.01
N disease immunohistochemistry staining (positive vs negative)	17 vs 24	8 vs 21	0.001
Resection margin and N disease conventional staining (positive vs negative)	24 vs 17	9 vs 23	0.001
Resection margin and N disease immunohistochemistry staining (positive vs negative)	29 vs 12	8 vs >36	<0.0001

[a] Analysis for 40 patients.

asbestos exposure, chest pain, dyspnea, cough, cell type (epithelial versus biphasic and sarcomatous), involved resection margins, and N stage. Significance was evaluated with the log rank test and less than 0.05 was considered the threshold value. Significant variables at univariate analysis were entered into Cox regression analysis to select the most predictive ones.

Results

Histologic examination revealed 34 epithelioid, 4 biphasic, and 3 sarcomatoid subtypes. All primitive tumors were positive for either calretinin or mesothelin. Preoperative cervical mediastinoscopy was performed in 10 of these patients. In this setting, the lymph node mean diameter was 1.7 ± 0.6 cm: none showed microscopic evidence of N disease, although two were fond to be positive at subsequent thoracotomy. Results of postoperative TNM staging were that 14 patients were in stage I, 6 were in stage II, and 21 were in stage III. Distribution of T stage and N disease as well as main prognostic factors investigated are summarized in Table 1.

We experienced only one 30-day perioperative mortality caused by pulmonary embolism. This patient was excluded from the survival analysis. The median follow-up interval was 14 months (range, 0.2 to 44 months) with a median survival of 13 months. Twenty-eight patients (68%) died of disease after a local (n = 21 of 28, 75%) or distant relapse (n = 7 of 28, 25%). Another 2 died of pulmonary failure subsequent to acute pneumonia. Main prognostic variables, including age greater than or equal to 65 years, cigarette use, asbestos exposure, chest pain, dyspnea, cough, side of tumor, and chemotherapy regimen did not significantly associate with survival duration. Univariate analysis identified four significant variables associated with poorer prognosis: nonepithelial histology ($p = 0.001$), TNM stage ($p = 0.007$), positive resection margins ($p = 0.002$), and N disease ($p = 0.01$).

The 16 patients with positive resection margins had a 2-year survival of 13% compared with the 25 patients with negative resection margins who had a 2-year survival of 49%. Furthermore, the 12 patients with metastatic lymph nodes and the 29 with negative nodes presented a 2-year survival of 8% and 44%, respectively.

Immunohistochemistry allowed the identification of 6 patients with occult positive resection margins (Tables 1, 2), thus increasing the prognostic significance of the variable ($p < 0.0001$; Fig 1). No significant superiority between antigens was detected (data not shown). The median postoperative survival of patients with microinfiltration of resection margins was 9 months (95% confidence interval, 7.5 to 10.4), significantly less than those without residual disease, which was 22 months (95% confidence interval, 20.6 to 31.0). Interestingly, the probability of discovering occult metastases was not correlated with a higher T stage (Table 2) in contrast with the

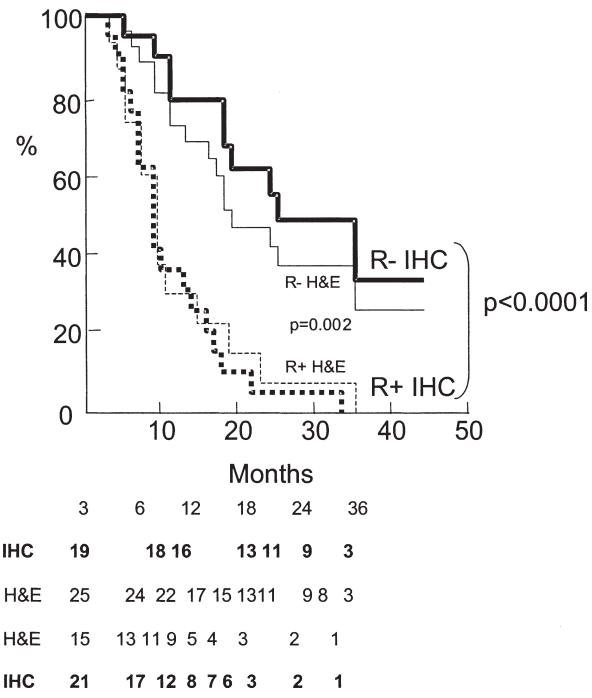

Fig 1. Resection margin revised by immunohistochemistry (IHC). Overall survival curve according to positive (R+) or negative (R−) resection margin assessed with conventional hematoxylin and eosin (H&E) staining and with immunohistochemistry.

Table 2. Patients' Distribution Pattern of Residual Disease on Resection Margins Evaluated With Conventional Hematoxylin and Eosin Staining and Immunohistochemistry

Variable	Resection Margin Assessment H&E (no. patients)	Further Residual Assessment IHC (no. patients)
PT1 stage (n = 19)	8	5
PT2 stage (n = 12)	5	1
PT3 stage (n = 10)	3	...
Posterior parietal pleura[a]	2	1
Posterior costophrenic sinus	3	1
Vertebral groove	2	...
Lateral parietal pleura	2	...
Lateral costophrenic sinus	4	...
Anterior parietal pleura	2	1
Anterior costophrenic sinus	4	1
Pericardiophrenic sinus	1	...
Anterior mediastinal pleura	3	...
Posterior mediastinal pleura	4	...
Chest wall	2	...
Bronchial stump	3	1
Pericardium	3	1
Diaphragm	2	1
TOTAL (n = 41)	16	6

[a] Patients with more than one site.

H&E = hematoxylin and eosin staining; IHC = immunohistochemistry.

Table 3. Patients' Nodal Disease Pattern Evaluated With Conventional Hematoxylin and Eosin Staining and Immunohistochemistry

	Nodal Assessment H&E		Further Nodal Metastases Discovered by IHC	
	No. Patients	Size (mean ± SD, cm)	No. Patients	Size (mean ± SD, cm)
N disease negative (patients)	29	1.1 ± 0.2	...	...
N disease positive (patients)	12	1.3 ± 0.9	5	1.1 ± 0.5
Retrieved by mediastinoscopy	...	...	2	1.5 ± 0.6
Upper tracheal[a]	1	1.2 ± 0.3	4	1.2 ± 0.4
Lower tracheal[a]	2	1.5 ± 0.2	5	1.3 ± 0.3
Subcarinal[a]	5	1.6 ± 0.4	...	...
Anterior mediastinal[a]	3	1.2 ± 0.3	...	...
Paraesophageal[a]	2	1.2 ± 0.2	2[b]	1.2 ± 0.3

[a] Patients with more than one station. [b] These 2 patients had other positive stations accessible to mediastinoscopy.

H&E = hematoxylin and eosin staining; IHC = immunohistochemistry; SD = standard deviation.

expectation that the more elevated the T stage the greater the possibility of leaving tumor cells. The costophrenic sinus, either anterior or posterior, represented the most frequent site of occult residual disease (Table 2).

Microscopic N disease was discovered in 5 patients. All these patients presented at least one positive station located in the upper mediastinum that could have been reached by cervical mediastinoscopy (Table 3). Interestingly, in 2 of these patients, the lymph nodes harvested during cervical mediastinoscopy were negative at conventional staining but revealed positivity after immunohistochemical reassessment. The presence of metastases was not correlated with lymph node size: negative node median diameter was not significantly different from the positive ones (Table 3). The survival curve according to the immunohistochemical N disease reassessment was more significant ($p = 0.001$; Fig 2). The median postoperative survival of patients with lymph node metastases was 8 months (95% confidence interval, 6.3 to 9.4) significantly less than those without node metastases, which was 21 months (95% confidence interval, 19.6 to 29.0).

Combining the two variables reassessed by immunohistochemistry, we discovered 5 new patients with occult disease, 2 patients with positive resection margin only, 1 with positive node only, and 2 with both. The other 2 patients with newly discovered resection margin had positive lymph nodes at conventional staining, and the remaining 2 with nodal micrometastases had already yielded positive results at resection margin evaluation. In this way the significance reached a very high level in overall survival ($p < 0.0001$; Table 1). Figure 3 showed that patients found positive (margin plus nodes) only at immunostaining have a similar survival to those positive at conventional technique.

At Cox regression analysis, the combined resection margin and nodal status reassessed by immunohistochemistry was selected as the most significant prognosticator ($p < 0.0001$; odds ratio, 5.4; 95% confidence interval, 3 to 15).

Comment

Extrapleural pneumonectomy remains a cornerstone of the multimodality treatment of malignant pleural mesothelioma. This is valid for the classic trimodality approach pioneered by Sugarbaker and colleagues [15], for the neoadjuvant chemotherapy strategy proposed by Weder and associates [5], and for the intensity-modulated adjuvant radiotherapy established by Rice and coworkers [16]. Nonetheless, results achieved are not yet satisfying, and median survival is quite low. In the

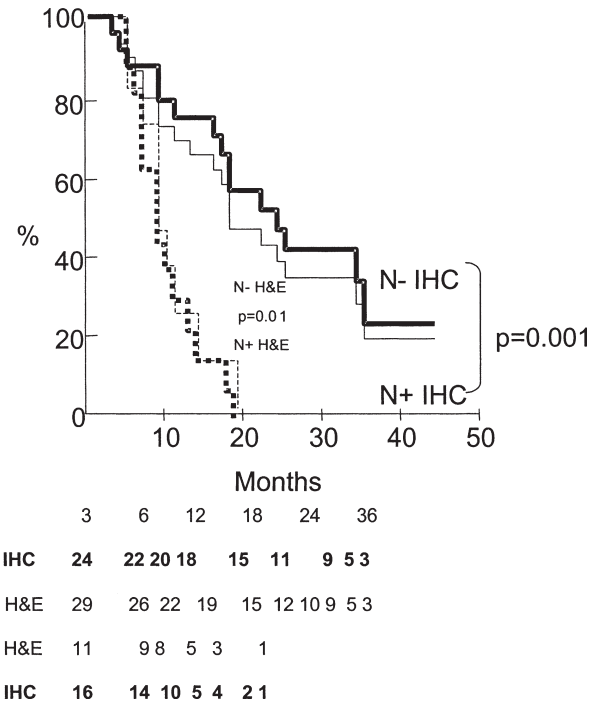

Fig 2. N disease revised by immunohistochemistry (IHC). Overall survival curve according to N positive (N+) or negative (N−) disease assessed with hematoxylin and eosin (H&E) staining and with immunohistochemistry.

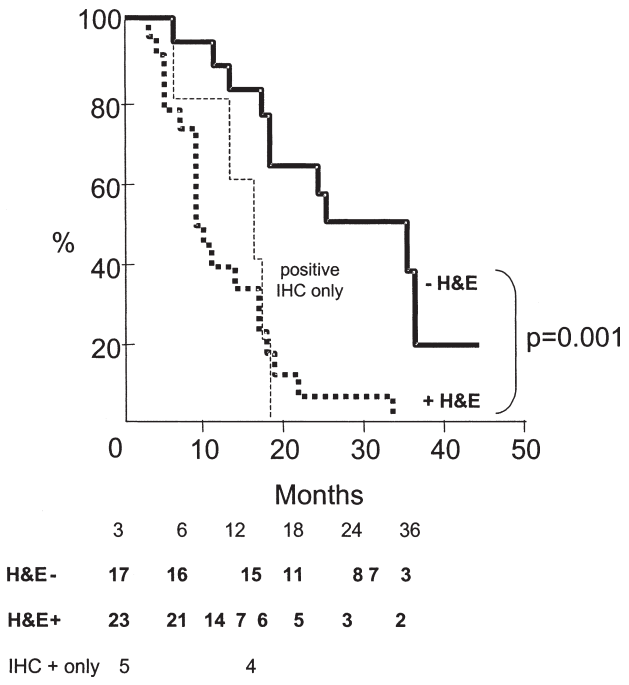

Fig 3. Conventional versus positive only at immunohistochemistry (IHC+). Overall survival curve according to combined resection margin and N disease positive (H&E+) or negative (H&E−) at hematoxylin and eosin (H&E) staining compared with patients found positive only at immunostaining. Survival curve has a similar trend.

large series of 176 patients reported by Sugarbaker and associates [4], the general median survival time was 19 months. Nonepithelial histologic subtype, residual tumor at the resection margins, and extrapleural metastatic lymph nodes are indicated as the main reasons for the failure of extrapleural pneumonectomy [3–12].

On the basis of recent progress in immunohistochemical techniques for detection of occult neoplastic disease and analogous experiences in other neoplasms [13], we decided to reassess infiltration of resection margins and lymph node metastasis. Indications from the literature [14] have led us to use monoclonal antibodies against specific mesothelioma markers such as calretinin and mesothelin. The resection margin evaluation of an extrapleural pneumonectomy per se represents a great challenge. In fact, the surface to be examined is so extended that even the most accurate pathologic examination cannot be considered totally reliable. According to Sugarbaker and colleagues [4], we have already adopted a compromise solution by selecting areas with obvious macroscopic infiltration, with a high infiltration risk (ie, bronchus, pericardium, diaphragm), and some specific areas of the parietal pleura for classic microscopic studies. The same paraffin-embedded specimens were reassessed with immunohistochemistry for the present study.

In our series, the traditional histologic examination already evidenced the positive resection margin and the nodal status, together with the histologic type, as the sole significant prognostic factors. Nevertheless, the reassessment with immunohistochemistry contributed to demonstrate the presence of occult disease in 5 new patients, which represented almost 15% of our study group. The survival curve, according to the new reassessment, was more significant ($p < 0.0001$). Interestingly, we found that the probability of discovering occult metastases was not correlated with a higher T stage. This contradicts the diffuse opinion that a more elevated T stage may increase the risk of leaving tumoral cells. We tried to explain this apparent paradox by the fact that a lower T stage may favor a less full-thickness resection, increasing the possibility of leaving tumor areas. Indeed, the anterior or posterior costophrenic sinus, which is the more difficult site to access by lateral thoracotomy, was the most frequent site of occult residual disease.

Extrapleural lymph node metastases are detectable from 28% to 52% of all the patients undergoing extended surgery [4, 6, 11, 12, 15] and are related to a significantly poorer prognosis after radical resection [4, 6, 12, 17]. In our series, they represented 15%, increasing to 34% when using immunohistochemical staining.

In accordance with Prenzel and coworkers [18], we also found that the long-axis diameter of lymph nodes containing metastatic tumor is not significantly different from those free of tumor. Because lymph node size is not significantly different when involved by metastatic mesothelioma, preoperative imaging using size criteria will be unreliable for staging extrapleural lymph node metastasis, and this justifies the low results in patient selection achieved by positron emission tomography [19, 20]. Thus, we reaffirmed the role of preoperative cervical mediastinoscopy in patient candidates to extended radical resection in malignant pleural mesothelioma. Most positive mediastinal lymph nodes are accessible to mediastinoscopy [6, 9, 21]. On the other hand, the probability of positive nodes not accessible to mediastinoscopy is quite low [4, 22]. In our series, in all patients metastatic lymph nodes were located in the upper mediastinum. Thus, they could all have potentially been accessible to mediastinoscopy. We also found that the use of immunohistochemical staining can improve the diagnostic accuracy of the test.

We acknowledge some limitations in our study. The main limitation relies on its retrospective nature and the relatively limited sample size. However, it must be noted that immunohistochemistry reassessment of all specimens was achieved in a limited period with the same technique and by the same pathologist. Moreover, although the study covers a period of 20 years and multimodality treatments are slightly different owing to the long time span, the surgical procedure was performed according to the same criteria and by the same surgeon. Another limitation can be represented by the method in assessing resection margins, but this is the same method used in other qualified institutions.

In conclusion, we affirm that extrapleural pneumonectomy can be performed with an acceptable low mortality rate in multimodality therapy of selected patients with malignant pleural mesothelioma. The detection of occult disease in resection margins and N disease may allow a more accurate prediction of survival, thus influencing

surveillance and therapeutic strategies. Because N disease is a clear contraindication to mesothelioma resection, all patients considered for potential radical resection should undergo preoperative routine cervical mediastinoscopy and all specimens should be processed with immunohistochemical techniques.

We thank Giulia Musolino, MD, for her valuable contribution in editing this manuscript. This research was granted by the Italian Health Ministry (title of the project: "Profilo genetico associato al fenotipo metastatico e alla prognosi nei tumori polmonari"), and by a 60% grant in 2002 from the Tor Vergata University.

References

1. Peto J, DeCarli A, La Vecchia C, Levi F, Negri E. The European mesothelioma epidemic. Br J Cancer 1999;79:666–72.
2. Flores RM, Rusch VW. Diffuse malignant mesothelioma. In: Shields T, ed. General thoracic surgery. Philadelphia: Lippincott Williams & Wilkins, 2005:901–21.
3. Steele JPC, Klabatsa A, Fennel DA, et al. Prognostic factors in mesothelioma. Lung Cancer 2005;49(Suppl 1):S49–52.
4. Sugarbaker D, Flores R, Jaklitsch M, et al. Resection margins, extrapleural nodal status and cell type determine postoperative long term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. J Thorac Cardiovasc Surg 1999;117:54–65.
5. Weder W, Kestenholz P, Taverna C, et al. Neoadjuvant chemotherapy followed by extrapleural pneumonectomy in malignant pleural mesothelioma. J Clinl Oncol 2004;22:3451–7.
6. Rusch VW, Venkatraman ES. Important prognostic factors in patients with malignant pleural mesothelioma, managed surgically. Ann Thorac Surg 1999;68:1799–804.
7. Schil PV. Malignant pleural mesothelioma: staging systems. Lung Cancer 2005;49(Suppl 1):S45–8.
8. Rusch VW. A proposed new international TNM-staging system for malignant pleural mesothelioma: International Mesothelioma Interest Group. Chest 1995;108:1122–8.
9. Pilling JE, Stewart DJ, Martin-Ucar AE, Muller S, O'Byrne KJ, Waller DA. The case of routine cervical mediastinoscopy prior to radical surgery for malignant pleural mesothelioma. Eur J Cardiothorac Surg 2004;25:497–501.
10. Rice DC, Erasmus JJ, Craig WS, et al. Extended surgical staging for potentially resectable malignant pleural mesothelioma. Ann Thorac Surg 2005;80:1988–93.
11. Edwards JG, Stewart DJ, Martin-Ucar A, Muller S, Richards C, Waller DA. The pattern of lymph node involvement influences outcome after extrapleural pneumonectomy for malignant mesothelioma. J Thorac Cardiovasc Surg 2006;131:981–7.
12. De Perrot M, Uy K, Anraku M, et al. Impact of lymph node metastasis on outcome after extrapleural pneumonectomy for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2007;133:111–6.
13. Mineo TC, Ambrogi V, Pompeo E, Baldi A. Immunohistochemistry-detected microscopic tumor spread affects outcome in en-bloc resection for T3-chest wall lung cancer. Eur J Cardiothorac Surg 2007;31:1120–4.
14. Ordonez NG. The immunohistochemical diagnosis of mesothelioma: a comparative study of epithelioid mesothelioma and lung adenocarcinoma. Am J Surg Pathol 2003;27:1031–51.
15. Sugarbaker DJ, Heher EC, Lee TH, et al. Extrapleural pneumonectomy, chemotherapy and radiotherapy in the treatment of diffuse malignant pleural mesothelioma. J Thorac Surg Cardiovasc Surg 1991;102:10–5.
16. Rice DC, Stevens CW, Correa AM, et al. Outcomes after extrapleural pneumonectomy and intensity-modulated radiation therapy for malignant pleural mesothelioma. Ann Thorac Surg 2007;84:1685–92.
17. Edwards J, Abrams K, Leverment J, Spyt T, Waller D, O'Byrne K. Prognostic factors for malignant mesothelioma in 142 patients: validation of CALGB and EORTC prognostic scoring systems. Thorax 2000;55:731–5.
18. Prenzel K, Monig S, Sinning J, et al. Lymph node size and metastatic infiltration in non-small cell lung cancer. Chest 2003;97:1148–51.
19. Schneider DB, Clary-Macy C, Challa S, et al. Positron emission tomography with F18-fluorodeoxyglucose in the staging and preoperative evaluation of malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2000;120:128–33.
20. Flores RM, Akhurst T, Gonen M, et al. Positron emission tomography predicts survival in malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2006;132:763–8.
21. Maggi G, Casadio C, Cianci R, Rena O, Ruffini E. Trimodality management of malignant pleural mesothelioma. Eur J Cardiothorac Surg 2001;19:346–50.
22. Schouwink J, Kool L, Rutgers E, et al. The value of chest computer tomography and cervical mediastinoscopy in the preoperative assessment of patients with malignant pleural mesothelioma. Ann Thorac Surg 2003;75:1715–9.

The Value of Occult Disease in Resection Margin and Lymph Node After Extrapleural Pneumonectomy for Malignant Mesothelioma

Tommaso Claudio Mineo, Vincenzo Ambrogi, Eugenio Pompeo, Alfonso Baldi, Franco Stella, Paolo Aurea and Mario Marino

Ann Thorac Surg 2008;85:1740-1746
DOI: 10.1016/j.athoracsur.2008.01.088